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Role of Barium(II) in the Determination of the Absolute Configuration of Chiral Amines by ^{1}H NMR Spectroscopy

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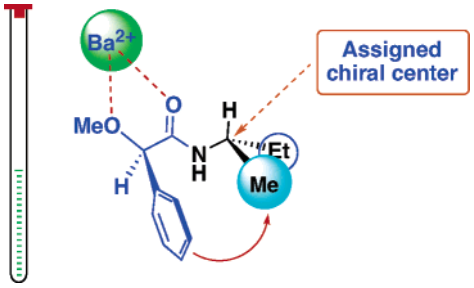

The assignment of the absolute configuration of α-chiral primary amines by complexation of their MPA derivatives with Ba^{2+} and NMR analysis of the changes generated is presented. All that is required is (a) the derivatization of the amine of unknown configuration with one enantiomer of the auxiliary reagent (MPA), either (*R*) or (*S*)-α-methoxyphenylacetic acid, (b) the recording of the ^{1}H NMR spectrum of the resulting amide in MeCN-d_3, (c) the addition of $Ba(ClO_4)_2$ to the NMR tube, and (d) the recording of a second spectrum after a few minutes of shaking. The above steps take a few minutes and are followed by an analysis of the shifts (measured as $\Delta\delta^{Ba}$) produced on the L_1 and L_2 substituents of the amine by the addition of Ba^{2+} and their comparison with those expected from the conformational changes produced by the complexation. The conformational changes initiated by complexation have been subjected to NMR and CD studies, which showed that the formation of the complex shifts the equilibrium from an antiperiplanar (AP) to a synperiplanar (SP) form, leading to an increase of the shielding by the phenyl group of MPA of the substituent of the amine located on the same side. In addition, theoretical calculations [density functional theory (DFT)] provide further support for the formation, structure, and stability of the complexes. The general applicability of this method and the trustworthiness of the resulting configurational assignment were guaranteed with a series of amines of known absolute configuration and varied structures, used as test compounds. The method proposed is simple, fast, and inexpensive, and it requires a very small amount of sample, only one derivatization, and the recording of just two ^{1}H NMR spectra at room temperature. A graphical guide to simplify the application of this method is included.

Introduction

The configurational assignment of chiral compounds in solution based on ^{1}H NMR spectroscopy has become a well-established field of chemistry because of the impressive development reached in the past decade. As originally developed by Mosher,[1] this approach resorted to just an auxiliary reagent (α-methoxyphenyl acetic acid, MTPA, **1**) that could be applied to secondary alcohols and primary amines. Currently, the expansion experienced by this methodology has provided researchers with new and more effective reagents that can be applied to a variety of families of chiral substrates, such as carboxylic acids, primary alcohols, diols, and, importantly, has made available to those researchers an understanding of the physical and chemical foundations of the method.[2]

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(1) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519. (b) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143−2147.

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This knowledge about the chemical behavior of the various auxiliary reagent/chiral substrate systems also allowed new ways of simplifying the experimental procedure to be devised. Thus, the usual approaches that required the use of two enantiomers of the auxiliary reagent gave way to methods that required the use of just a single enantiomer of the reagent and only one-half the amount of substrate sample.[3] The recent introduction of solid-matrix-bound reagents has also contributed to these efforts focused on making configuration determination an easier task.[4]

In the case of chiral secondary alcohols, there are two ways to determine the absolute configuration using a single derivative. They involve the controlled manipulation of the conformational equilibrium of an α-methoxyphenylacetic acid (MPA, **2**) ester derivative. In one case,[3a] this is achieved simply by varying the NMR probe temperature: the recording of two NMR spectra at different temperatures reflects the variation of the populations of the main conformers (synperiplanar, SP, and antiperiplanar, AP) of the MPA ester, and this allows the absolute configuration to be inferred by observing the selective shielding effects produced on the substrate. In the other method,[3c] the in situ complexation of the α-methoxyphenylacetic acid (MPA) ester derivative with barium(II) induces conformational changes that modify the chemical shifts of the alcohol part in a predictable way and, therefore, allow the configuration to be deduced. In both cases, theoretical studies and independent experimental evidence such as circular dichroism results, give fully satisfactory explanation to the effects observed.

In the case of primary amines, the complexity of the conformational equilibria with either MTPA or MPA amide derivatives[3] impedes the use of the approach based on temperature variation. Therefore, double derivatization procedures are still operative to elucidate the configuration of primary amines with the stereogenic center in the α position. Although classical auxiliary reagents (MTPA, MPA) are still employed for this task,[1b,5,6] more effective reagents such as Boc-phenylglycine (BPG, **3**) have been introduced in recent years.[7]

We now present our results on the use of barium(II) complexes generated in the NMR tube containing only one MPA amide [either (*R*) or (*S*)]. A short communication describing just the experimental technique and protocols has already been published.[8] In this article, we present theoretical (DFT calculations) and experimental (NMR and CD) data that provide a detailed explanation and rationalization for the observed NMR effects and the role of Ba^{2+} in the conformational population dynamics, in how this affects the NMR spectra, and in the differences observed between MPA amides and MPA esters. The reliability, scope, and limitations of this method for the assignment of the absolute configuration of a chiral amine by NMR spectroscopy of a single derivative are studied with a wide range of structurally diverse amines. To facilitate the use of this procedure, a chart for users has been incorporated at the end of this article.

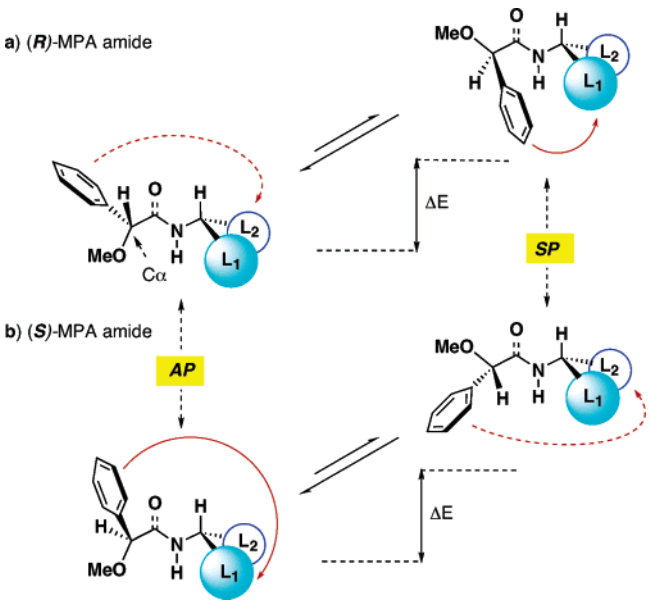


FIGURE 1. Equilibrium between the two main conformers of (a) an (*R*)-MPA amide and (b) an (*S*)-MPA amide [AP = antiperiplanar (major); SP = synperiplanar (minor)]. Red curved arrows indicate the anisotropic effect caused by the phenyl group on L_1/L_2 in each conformer.

Results

1. NMR Studies: Addition of a Barium(II) Salt to MPA Amides. Extensive theoretical calculations (MM, semiempirical, and ab initio) and DNMR experiments have shown that, in solution, arylmethoxyacetic acid amides (i.e., MPA amides) exist mainly as two conformers in equilibrium.[5] The major conformer, denoted AP, has the Cα—OMe and the C═O bonds *antiperiplanar*. In the minor conformer, denoted SP, these bonds are *synperiplanar*. In both conformers, the aryl ring is virtually coplanar with the Cα—H bond (Figure 1). It is worth pointing out that this conformational preference in arylmethoxyacetic acid amides is opposite to that of arylmethoxyacetic acid esters. In the latter, the SP conformers are the most populous.

According to these studies, in an (*R*)-MPA amide, L_2 is shielded by the phenyl group in the more stable AP conformer, whereas L_1 is shielded in the less stable SP conformer (Figure 1a). The opposite situation holds for the (*S*)-MPA amide (Figure 1b). As a result, the NMR signal corresponding to L_2 is more shielded by the phenyl group in the (*R*)- than in the (*S*)-MPA amide. The difference between the chemical shifts of L_2, when the NMR spectra of both diasteromeric amides are compared, is expressed as a negative $\Delta\delta^{RS}$ value.[9] In the other hand, L_1 is more heavily shielded in the (*S*)- than in the (*R*)-MPA amide, and accordingly, its $\Delta\delta^{RS}$ magnitude is expressed as a positive value.

The MPA amides of (−)-isopinocampheylamine[10] (**4**) reflect these facts. The phenyl group in the more stable AP conformer

(2) (a) Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17−117. (b) Seco, J. M.; Quiñoá, E.; Riguera, R. *Tetrahedron: Asymmetry* **2001**, *12*, 2915−2925.

(3) (a) Latypov, Sh. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Am. Chem. Soc.* **1998**, *120*, 877−882. (b) Seco, J. M.; Quiñoá, E.; Riguera, R. *Tetrahedron* **1999**, *55*, 569−584. (c) García, R.; Seco, J. M.; Vázquez, V.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **2002**, *67*, 4579−4589.

(4) Porto, S.; Durán, J.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Org. Lett.* **2003**, *5*, 2979−2982.

(5) (a) Latypov, Sh. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1995**, *60*, 1538−1545. (b) Seco, J. M.; Latypov, Sh. K.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1997**, *62*, 7569−7574.

(6) Trost, B. M.; Bunt, R. C.; Pulley, S. R. *J. Org. Chem.* **1994**, *59*, 4202−4205.

(7) Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1999**, *64*, 4669−4675.

(8) López, B.; Quiñoá, E.; Riguera, R. *J. Am. Chem. Soc.* **1999**, *121*, 9724−9725.

(9) The $\Delta\delta^{RS}$ value for a proton is the difference between its chemical shift in the (*R*) derivative and its chemical shift in the (*S*) derivative.

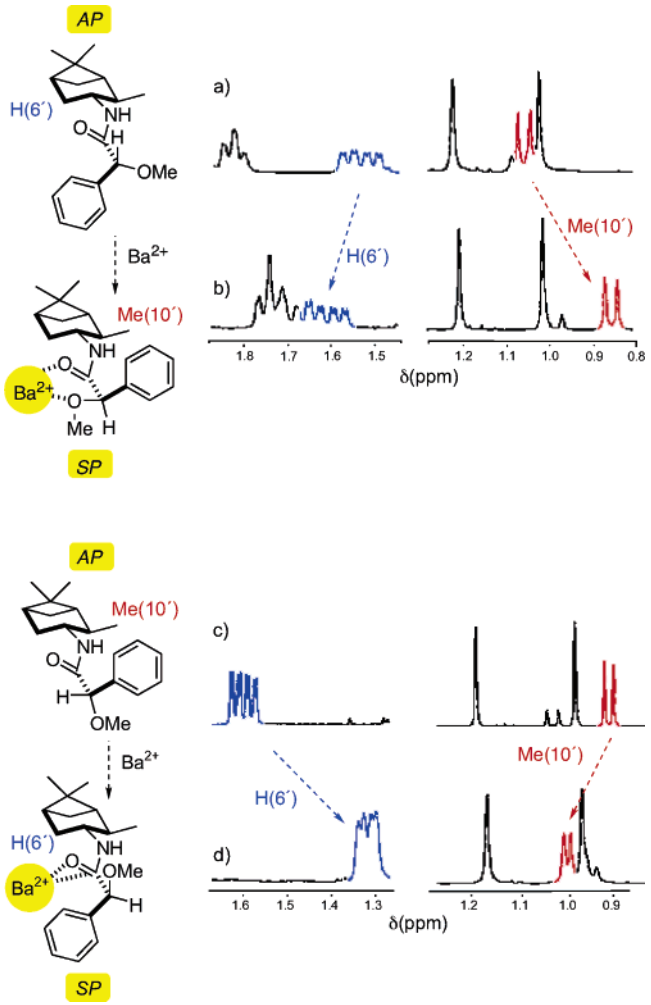


FIGURE 2. Partial ^{1}H NMR spectrum of the (*R*)-MPA amide of (−)-isopinocampheylamine (a) before and (b) after addition of barium(II). Partial ^{1}H NMR spectrum of the (*S*)-MPA amide of (−)-isopinocampheylamine (c) before and (d) after addition of barium(II).

of the (*R*)-MPA amide shields the H(6′) protons, whereas the same group shields CH_3(10′) in the less stable SP conformer (Figure 2a). In the (*S*)-MPA amide, the situation is the opposite: CH_3(10′) is shielded in the more stable AP conformer, whereas the H(6′) protons are shielded in the less stable SP form (Figure 2c). The overall result is that the H(6′) protons are more shielded by the phenyl group in the (*R*)- than in the (*S*)-MPA amide, giving rise to negative $\Delta\delta^{RS}$ values [−0.075 and −0.053 ppm for H(6′ax) and H(6′eq), respectively], whereas the opposite situation holds for CH_3(10′) (a positive $\Delta\delta^{RS}$ value, +0.108 ppm).

To check whether a controlled modification of the equilibrium, useful for configurational assignment, could be possible by selective formation of a complex with an adequate metal ion, salts of Li^+, Na^+, K^+, Cs^+, Mg^{2+}, Ca^{2+}, and Ba^{2+} were added to NMR tubes containing the (*R*)-MPA amide of (−)-isopinocampheylamine in MeCN-d_3 (progressive additions of salt ranging from 1 equiv to saturation). The salts of the monovalent cations produced no observable shifts in the ^{1}H NMR spectra, whereas those of Mg^{2+}, Ca^{2+}, and Ba^{2+} induced visible changes in the chemical shifts of the substrate moiety. In fact, Ba^{2+} generated the largest shifts, when added either as its perchlorate or as iodide salt, and it was selected for this study. In addition, MeCN-d_3 was selected as the solvent of choice after proving to be the most adequate among several deuterated solvent systems tested.

Thus, when NMR spectra of the (*R*)- and the (*S*)-MPA amides of (−)-isopinocampheylamine (**4**) were recorded in MeCN-d_3 saturated with $Ba(ClO_4)_2$, significant changes (measured as $\Delta\delta^{Ba}$ values)[11] with respect to the spectra recorded in the absence of the salt (see above) were observed. These can be summarized as follows: (a) In the (*R*)-MPA amide, the signals corresponding to H(6′ax) and H(6′eq) shifted downfield upon addition of Ba^{2+} ($\Delta\delta^{Ba}$ = −0.07 and −0.11 ppm, respectively), whereas the signal generated by CH_3(10′) experienced an upfield shift ($\Delta\delta^{Ba}$ = +0.20 ppm), as shown in Figure 2a,b. (b) In the (*S*)-MPA amide, the shifts upon addition of Ba^{2+} were in the opposite directions to the above [$\Delta\delta^{Ba}$ = +0.27 and +0.05 ppm for H(6′ax) and H(6′eq), respectively; $\Delta\delta^{Ba}$ = −0.09 ppm for CH_3-(10′)], as shown in Figure 2c,d.

These changes can be ascribed to a redistribution of the populations of the AP and SP conformers in equilibrium, induced by the presence of the barium(II) salt. The process would be similar to the one observed in MPA esters.[3c,12] To be precise, in the case of an MPA amide, as the concentration of barium(II) increases, the less stable SP conformer becomes more populated because of the formation of a complex among the divalent metal and the two oxygens of the methoxy and carbonyl groups. Correspondingly, the population of the more stable AP conformer diminishes.

As a result, addition of the barium(II) salt to the (*R*)-MPA amide of (−)-isopinocampheylamine (**4**) increases the number of molecules in the SP conformation [CH_3(10′) under the shielding influence of the phenyl group], so in the average spectrum, the signal of this methyl group appears more shielded. On the other hand, the number of molecules in the AP conformation decreases, and consequently, the signals of the methylene group [H(6′ax) and H(6′eq) under the shielding influence of the phenyl group] experience a deshielding effect (Figure 2a,b).[13] A parallel analysis applies to the (*S*)-MPA amide, with opposite consequences for the shielding/deshielding of those groups (Figure 2c,d).

2. Effect of Barium(II) on the Conformational Equilibria of MPA Amides and MPA Esters as Shown by NMR Spectroscopy: A Comparison. A way to confirm whether the equilibrium present in MPA amides is modified by the metal cation, as suggested by the NMR experiments described above, consists of comparing the NMR behavior of an MPA amide and an MPA ester containing the same carbon skeleton [i.e., (*S*)-butan-2-amine (**5**) versus (*S*)-butan-2-ol (**6**)] when treated with barium(II). Because of the different conformer compositions of the two substrates (SP, main conformer in esters; AP, main conformer in amides; see Figure 3), the effect caused by the metal (selective stabilization of the SP conformer) should be the opposite for L_1 (methyl group) and L_2 (ethyl group) in the two cases.

(10) This amine was chosen as a model compound because it presents NMR signals that are easily identified.

(11) The $\Delta\delta^{Ba}$ value for a proton is the difference between its chemical shift before the addition of barium(II) and its chemical shift after the addition of barium(II).

(12) It is necessary to recall that, in MPA amides, the AP/SP equilibrium in the absence of barium is shifted in favor of AP, whereas in MPA esters, it is shifted toward SP.

(13) More detailed spectra of the (*R*)-MPA amide of (−)-isopinocampheylamine and the assignment of its configuration can be found in Figure 1-SI in the Supporting Information.

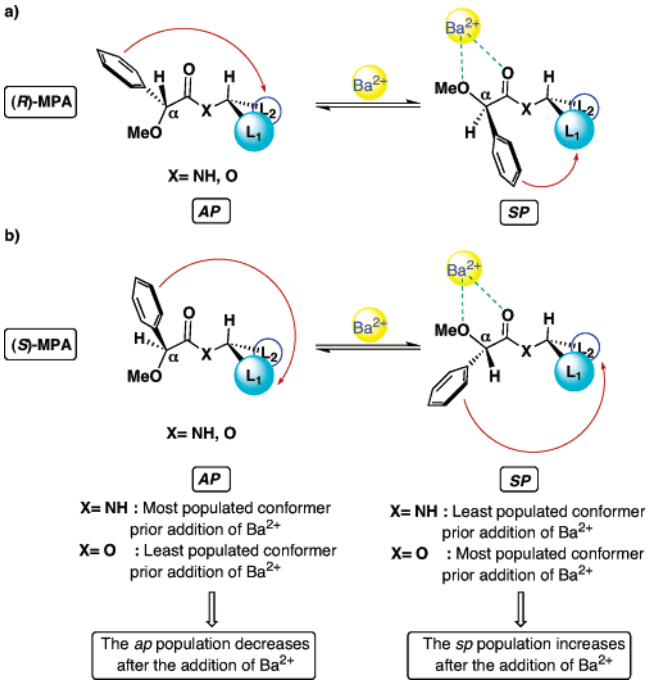


FIGURE 3. (a) Main conformers present in the equilibria of an (*R*)-MPA amide [X = NH; i.e., (*S*)-butan-2-amine (5)] and an (*R*)-MPA ester [X = O; i.e., (*S*)-butan-2-ol (**6**)] in the absence and in the presence of Ba^{2+}, as suggested from the NMR data. (b) The same for the corresponding (*S*)-MPA amide and ester.

In fact, this is the case when the NMR spectra are compared: The shifts strongly suggest that the ethyl group in the (*R*)-MPA amide is shielded in the AP conformer (more stable and populated), whereas in the (*S*)-MPA amide, the same group is shielded in the SP conformer (less stable and populated). In the (*R*)-MPA ester, the ethyl group is shielded in the AP conformer (less stable and populated), whereas in the (*S*)-MPA ester, it is shielded in the SP conformer (more stable and populated). The opposite reasoning holds for the methyl groups, as shown in Figure 3 (L_1= Me, L_2= Et). As a consequence, the ^{1}H NMR spectrum of the (*R*)-MPA amide is similar to the spectrum of the (*S*)-MPA ester, and the spectrum of the (*S*)-MPA amide is similar to the spectrum of the (*R*)-MPA ester[14] (Figure 4).

Interestingly, the ^{1}H NMR spectrum of the (*R*)-MPA amide *plus* barium(II) is similar to the spectrum of the (*R*)-MPA ester without barium(II), and the spectrum of the (*S*)-MPA amide *plus* barium(II) looks like the spectrum of the (*S*)-MPA ester without barium(II) (Figure 4). If we calculate the $\Delta\delta^{RS/Ba}$ values[15] for the protons of the amide and compare them with the $\Delta\delta^{RS}$ values for those of the ester, we obtain very similar values and identical signs (Table 1), strongly suggesting that the most representative NMR conformer, in both cases, must be the same SP conformer.

(14) The spectra should be alike but not identical because of the more effective shielding caused by the phenyl group in SP than in AP conformers, among other causes. The $\Delta\delta^{RS}$ values should have opposite signs in esters and amides, with smaller absolute values for the latter because of the predominance of the AP conformer. See ref 5a and also: Latypov, Sh. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1995**, *60*, 504−515.

(15) The $\Delta\delta^{RS/Ba}$ value for a proton is the difference between its chemical shift in the (*R*) derivative *with* barium(II) and its chemical shift in the (*S*) derivative *with* barium(II).

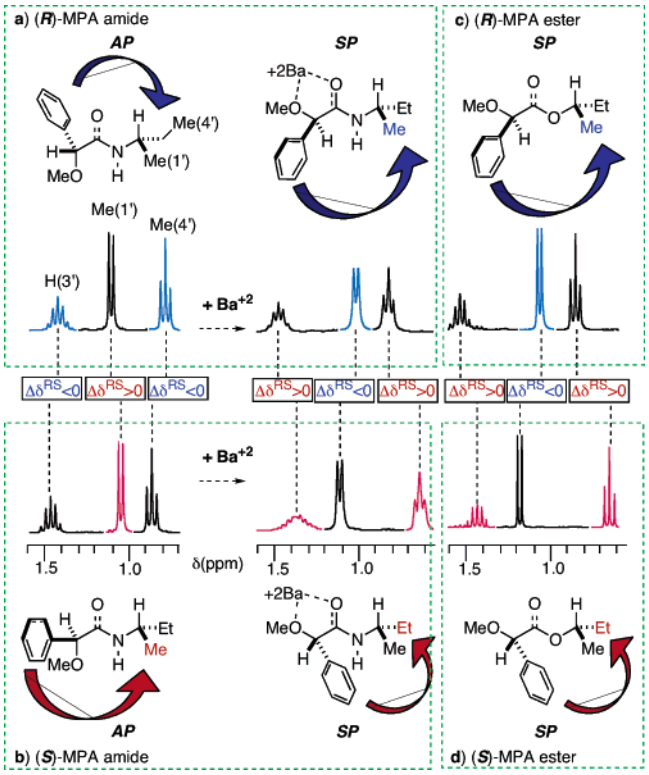
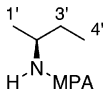
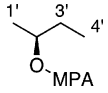


FIGURE 4. ^{1}H NMR spectra (MeCN-d_3) of (a) the (*R*)-MPA amide and (b) the (*S*)-MPA amide of (*S*)-butan-2-amine (**5**) without and with barium(II). ^{1}H NMR spectra (MeCN-d_3) of (c) the (*R*)-MPA ester and (d) the (*S*)-MPA ester of (*S*)-butan-2-ol (**6**) without barium(II).

TABLE 1. Chemical Shifts (Δ), $\Delta\delta^{RS}$ and $\Delta\delta^{RS/Ba}$ Values for the (*R*)- and (*S*)-MPA Derivatives of (*S*)-Butan-2-amine (5) and (*S*)-Butan-2-ol (6) (MeCN-d_3, 250 MHz)

			H(1′)	H(3′)	H(4′)
	(*R*)-MPA		1.111	1.433	0.781
	(*S*)-MPA		1.057	1.482	0.868
		$\Delta\delta^{RS}$	+0.054	−0.049	−0.087
	(*R*)-MPA + Ba^{2+}		1.005	1.468	0.813
	(*S*)-MPA + Ba^{2+}		1.100	1.352	0.624
		$\Delta\delta^{RS/Ba}$	−0.095	+0.116	+0.189
	(*R*)-MPA		1.057	1.544	0.840
	(*S*)-MPA		1.184	1.445	0.636
		$\Delta\delta^{RS}$	−0.127	+0.099	+0.204

3. CD Studies. Additional support for this interpretation of the NMR data was obtained from an independent technique such as CD. The CD spectra of (*R*)- and (*S*)-MPA amides show a Cotton effect at 226 nm associated to an $n-\pi$ transition of the carbonyl group. The Cotton effect is not affected by the chirality of the amine moiety, but it depends on the configuration at the asymmetric center of the auxiliary MPA: It is positive in the (*R*)-MPA amides and negative in the (*S*)-MPA amides. The octant rule[16] predicts opposite signs and a similar intensity for the AP and SP conformers [positive for the AP and negative for the SP conformer of an (*R*)-MPA derivative and the opposite behavior for an (*S*)-MPA derivative; Figure 5], and the intensity and the sign of this band in the average CD spectrum constitutes a measure of the AP/SP equilibrium. Thus, CD constitutes a

(16) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994.

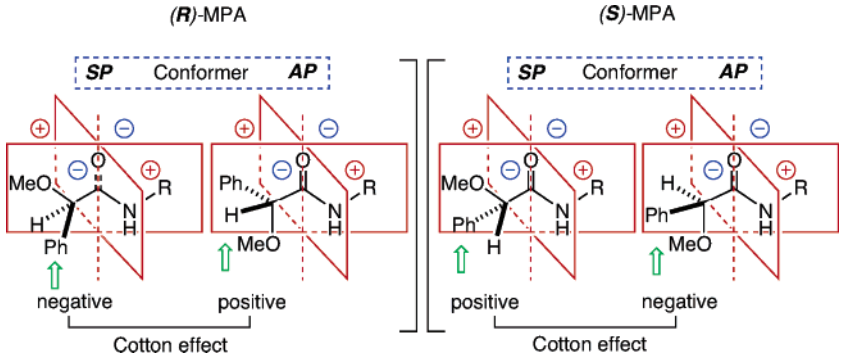


FIGURE 5. Cotton effects for the main conformers of MPA amides and octant rules. The sign of the Cotton effect is defined by the quadrant occupied by the phenyl group.

very useful technique for detecting the changes in the AP/SP ratio suggested by the NMR studies.

Strong evidence in favor of both the modification of the equilibrium by the divalent cation and the existence of Cotton effects of opposite signs for the two MPA conformers (SP/AP) was provided by the CD monitoring of the addition of barium(II) to the (*R*)-MPA ester of methanol (**7**) and to the (*R*)-MPA amide of methylamine (**8**). Prior to the addition, the Cotton effect of the ester is opposite to that of the amide, because although both exhibit the same chirality, the conformational compositions are different (SP is the major conformer in the MPA ester, and AP is the major conformer in the MPA amide). After the addition, the Cotton effect enhances its magnitude and keeps its negative sign in the case of the ester, suggesting an increase in the population of the major SP conformer. In the amide, the Cotton effect diminishes in magnitude keeping its positive sign, suggesting a decrease of the population of the AP conformer (Figure 6).

Further verification was obtained when a series of CD spectra of the (*R*)-MPA amide of (+)-bornylamine (**9**) were recorded in the absence and in the presence of increasing amounts of $Ba(ClO_4)_2$, and the following facts were observed: (a) In the absence of barium(II), the positive Cotton effect suggests the presence of a predominant AP conformer (Figure 7). (b) The addition of increasing amounts of barium(II) causes a decrease in the intensity of the positive Cotton band, indicating that the equilibrium is being modified and that the population of the SP conformer is growing, in full accordance with the NMR studies (Figure 7).

4. Additional NMR Studies. Both the CD and NMR experiments are coincident when pointing to the coordination of barium(II) to the oxygens of the methoxy and carbonyl groups as the cause of the increase of the SP populations and the corresponding responses in the spectra.

Additional experimental evidence that gives further support to this hypothesis is the following:

(a) In the ^{13}C NMR spectrum of the (*R*)-MPA amide of (*S*)-butan-2-amine (5), the carbonyl signal at 169.1 ppm shifts downfield to 171.4 ppm after the addition of the barium(II) salt (a 2.3 ppm shift). In the (*S*)-MPA amide, the shift is even larger, from 169.2 to 174.2 ppm (a 5.0 ppm shift). The increase of the electropositive character experienced by the sp^2 carbon atoms after the coordination of the carbonyl groups to the cation justifies these downfield shifts.

(b) In all of the compounds studied, no significant shifts were observed for the signals of the NH groups in the ^1H NMR

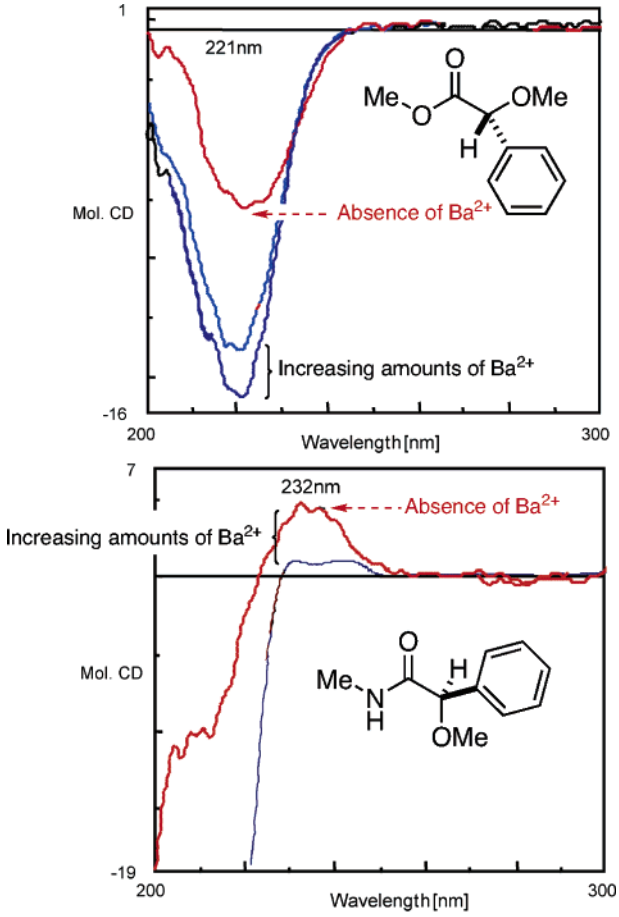


FIGURE 6. CD spectra of the (*R*)-MPA ester of methanol (**7**) and the (*R*)-MPA amide of methylamine (**8**) in the presence and in the absence of Ba^{2+} [$c = 10^{-3}$ M, $v = 300$ mL, MeCN, sequential additions of 10 mg of $Ba(ClO_4)_2$].

spectra after the addition of barium(II), strongly suggesting that these groups are not directly involved in the complexation processes.

(c) The signal corresponding to CαH of an MPA amide shifts downfield after the addition of barium(II), and the same phenomenon was observed for the MPA esters. The explanation can be found in the following fact: In the AP conformer, this proton lies in the shielding cone of the neighboring carbonyl group, whereas in the SP conformer, it lies in the deshielding zone (Figure 8). Therefore, a redistribution of the AP/SP populations in favor of the SP conformer can generate the

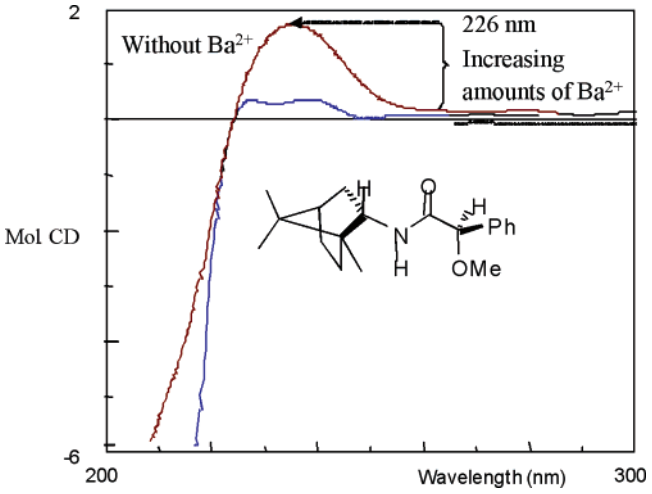


FIGURE 7. CD spectrum of the (*R*)-MPA amide of of (+)-bornylamine (**9**) in the presence of increasing amounts of Ba^{2+} [$c = 10^{-3}$ M, $v = 300$ μL, MeCN, sequential additions of 10 mg of $Ba(ClO_4)_2$].

observed downfield shift. For instance, −0.287 and −0.289 ppm downfield shifts are experienced by the (*R*)- and (*S*)-MPA amides of (−)-isopinocampheylamine (4). The shielding observed for the signal of the methoxy group is also consistent with the proposed AP/SP redistribution. This group is deshielded in the AP form and shielded in the SP form; thus, it moves upfield because of the increase in the SP conformer after complexation with barium(II) (Figure 8).

(d) The changes produced in the NMR spectra of the amides by addition of barium(II) were quantitatively monitored. Figure 9 shows the spectral evolution of a mixture of the (*R*)- and (*S*)-MPA amides of (*S*)-(+)-butan-2-amine (0.7 equiv and 0.3 equiv, respectively) in MeCN-d_3 during the addition of barium perchlorate. Before the addition, the $CH_3(1')$ signals are more shielded in the (*S*) than in the (*R*) derivative, whereas those of $CH_3(4')$ and $CH_2(3')$ are more shielded in the (*R*) than in the (*S*). The sequential addition of barium(II) changes the conformational preference, and correspondingly, the signals that previously were shielded in the (*R*) amide are now shielded in the (*S*) and vice versa.

(e) The determinations of stoichiometry and association constant (K_a) were undertaken from solution NMR data. The stoichiometry was calculated by means of the method of continuous variation (Job's method).[17] It involved preparing a series of solutions containing both the (*R*)-MPA amide of (+)-bornylamine (**9**) and barium perchlorate in varying proportions ($0 < [Ba^{2+}]_0/\{[Ba^{2+}]_0 + [(R)\text{-MPA amide}]_0\} < 1$) and where the total initial concentration of Ba^{2+} + (*R*)-MPA amide was constant for each solution. The chemical shift corresponding to H(6′ax) of the amide, which is sensitive to complex formation, was selected as the experimentally observed parameter. The data were plotted in the form $X_{(R)-\text{MPA amide}}\Delta\delta^{Ba}$ versus $X_{Ba^{2+}}$, and the position of the maximum indicated a 1:1 stoichiometry for the complex ($X_{Ba^{2+}} = 0.5$) (Figure 10a).

The association constant (K_a) was calculated according to the Benesi−Hildebrand (Hanna−Ashbaugh) treatment.[17a,18] The plot of $1/\Delta\delta^{Ba}$ [δH(6ax)] against $1/[Ba^{2+}]_0$ gave a linear representation with a slope $1/K_a\Delta\delta^{Ba}_{max}$ and intercept $1/\Delta\delta^{Ba}_{max}$, affording a value of $K_a = 5.39$ M^{-1} (Figure 10b).

5. Theoretical Calculations. Next, we decided to perform theoretical calculations to determine whether the conclusions about the formation of the complexes obtained from the experimental NMR and CD studies could be reproduced and confirmed by computational methods. The (*R*)-MPA amide of propan-2-amine (**10**) [(*R*)-*N*-isopropyl-2-methoxy-2-phenylacetamide] was chosen as a model compound, and the stability and structure of its complexes with Ba^{2+} were investigated.

First, a series of geometry optimizations was carried out by an appropriate selection of the initial values for the OCα−C=O, HN−CH, and MeO−CαC(=O) dihedral angles.

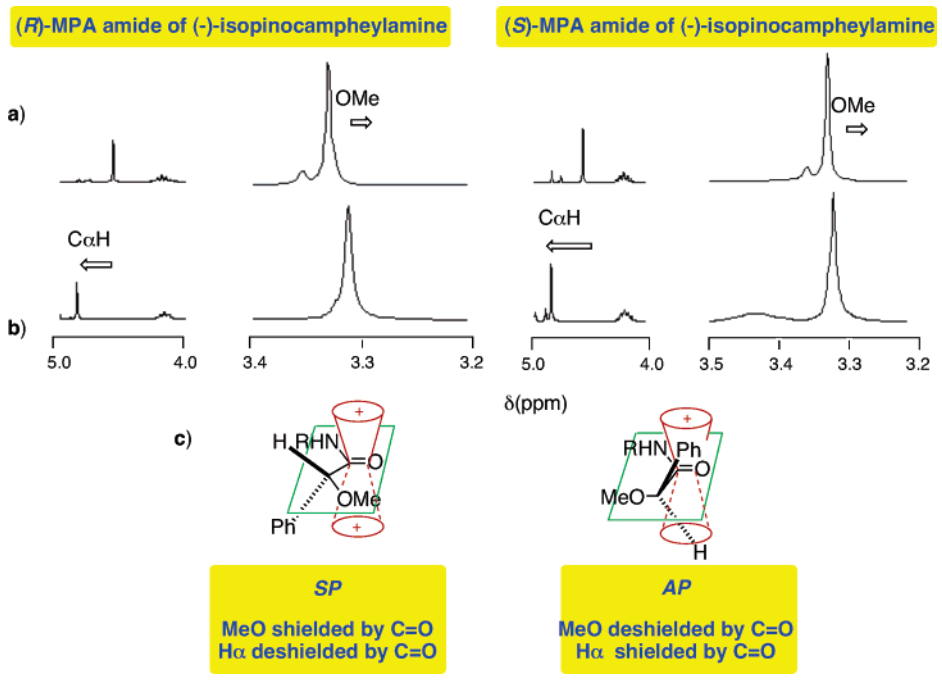


FIGURE 8. Effect of the shielding cone of the carbonyl group on the CαH and MeO groups of the (*R*)- and (*S*)-MPA amides of (−)-isopinocampheylamine (**8**) (a) before and (b) after the addition of Ba^{2+}.

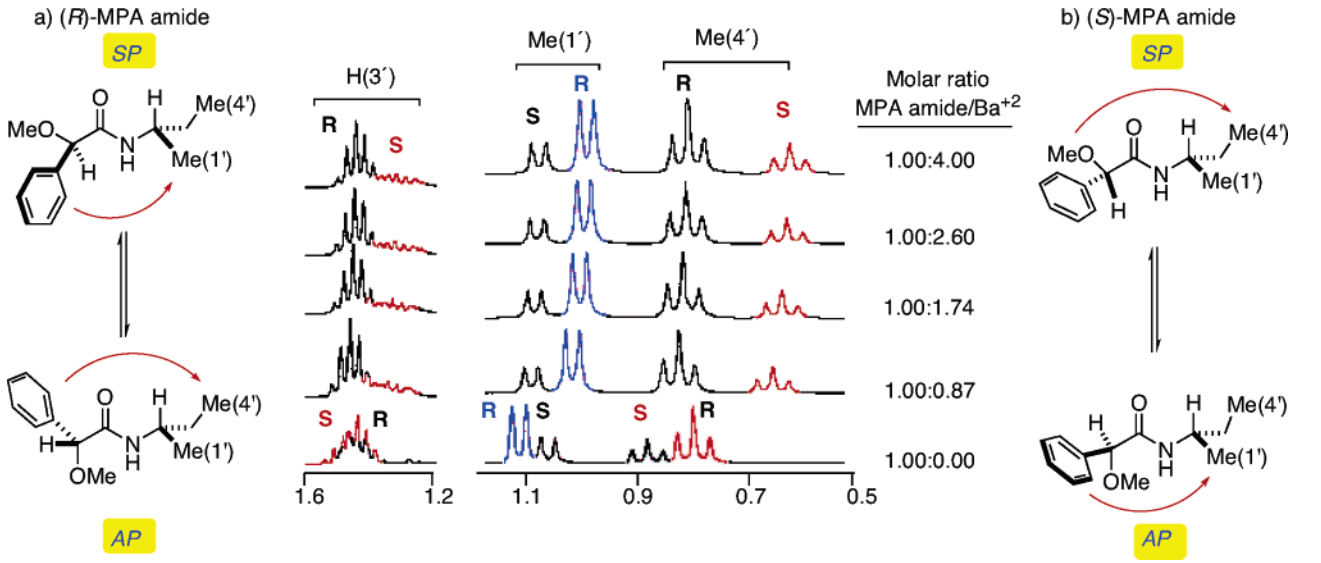


FIGURE 9. Evolution of the ^{1}H NMR spectra (250 MHz) of a mixture of (*R*)- and (*S*)-MPA amides of (*S*)-(+)-butan-2-amine (**5**) (0.7/0.3 equiv; MeCN-d_3) in the presence of increasing amounts of $Ba(ClO_4)_2$.

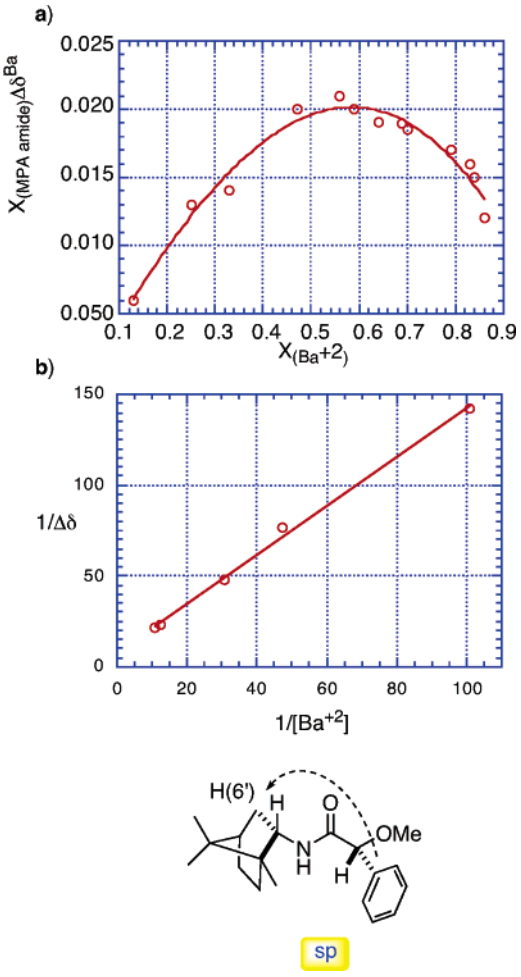


FIGURE 10. (a) Job plot for the determination of stoichiometry. (b) Benesi−Hildebrand data treatment for the determination of the association constant.

The phenyl group was placed in its preferred orientation as predicted in our previous work[3c] for the (*R*)-MPA ester of propan-2-ol. The relative energies and the values of the above torsion angles calculated for the optimized structures are detailed in Figure 11. The acronyms used to name the conformers include three pairs of letters, which refer to the classification of torsion angles proposed by Klyne and Prelog.[19] The first two (capital) letters refer to the OC−CO torsion angle, the two letters in the middle refer to the HN−CH torsion angle, and the last two letters refer to the MeO−CC(=O) dihedral angle.

At the B3LYP/LanL2DZ level of theory, all of the stable conformations in the gas phase present an antiperiplanar (AP) OCCO arrangement, and in all of these structures, a Me−O···H−N intramolecular hydrogen bond is exhibited. The present results contrast with those reported for the (*R*)-MPA ester of propan-2-ol,[3c] as the stabilities of the two different OC−C=O conformations of the ester were calculated to be rather similar. To a certain degree, the different behavior found here for the (*R*)-MPA amide of propan-2-amine arises from the hydrogen-bond interaction, which stabilizes the AP conformations. In addition, the effect of electron conjugation of the N atom on the carbonyl group, expected to be more pronounced than that of the O(−C=O) atom, can result in a significant negative partial charge on the carbonyl oxygen, which, in turn, destabilizes the SP OCCO arrangement.

The antiperiplanar (ap) orientation of the MeO−CC(=O) fragment is energetically favored over the (−)-synclinal (−sc) by about 0.7 kcal/mol. To a certain extent, this might be a consequence of the different strength of the hydrogen-bonding interactions in the ap and −sc MeO−CC(=O) arrangements, given that the O···H distance in the former conformation (∼2.0 Å) is about 0.2 Å shorter than that in the latter. As far as the orientation of the propan-2-amine moiety is concerned, the calculations predict that, in the gas phase, the synperiplanar (sp) arrangement is energetically disfavored by approximately 1.7 kcal/mol with respect to the ap and anticlinal (ac) arrangements.

For the gas phase, all attempts to optimize a conformation with a synperiplanar OC−CO arrangement were unsuccessful, and the optimizations led to AP conformations. However, SP conformations could be optimized when solvent effects, as calculated with the Onsager model, were taken into consideration. The reason for this is that the interaction with the medium is stronger for SP conformations (showing a dipole moment of

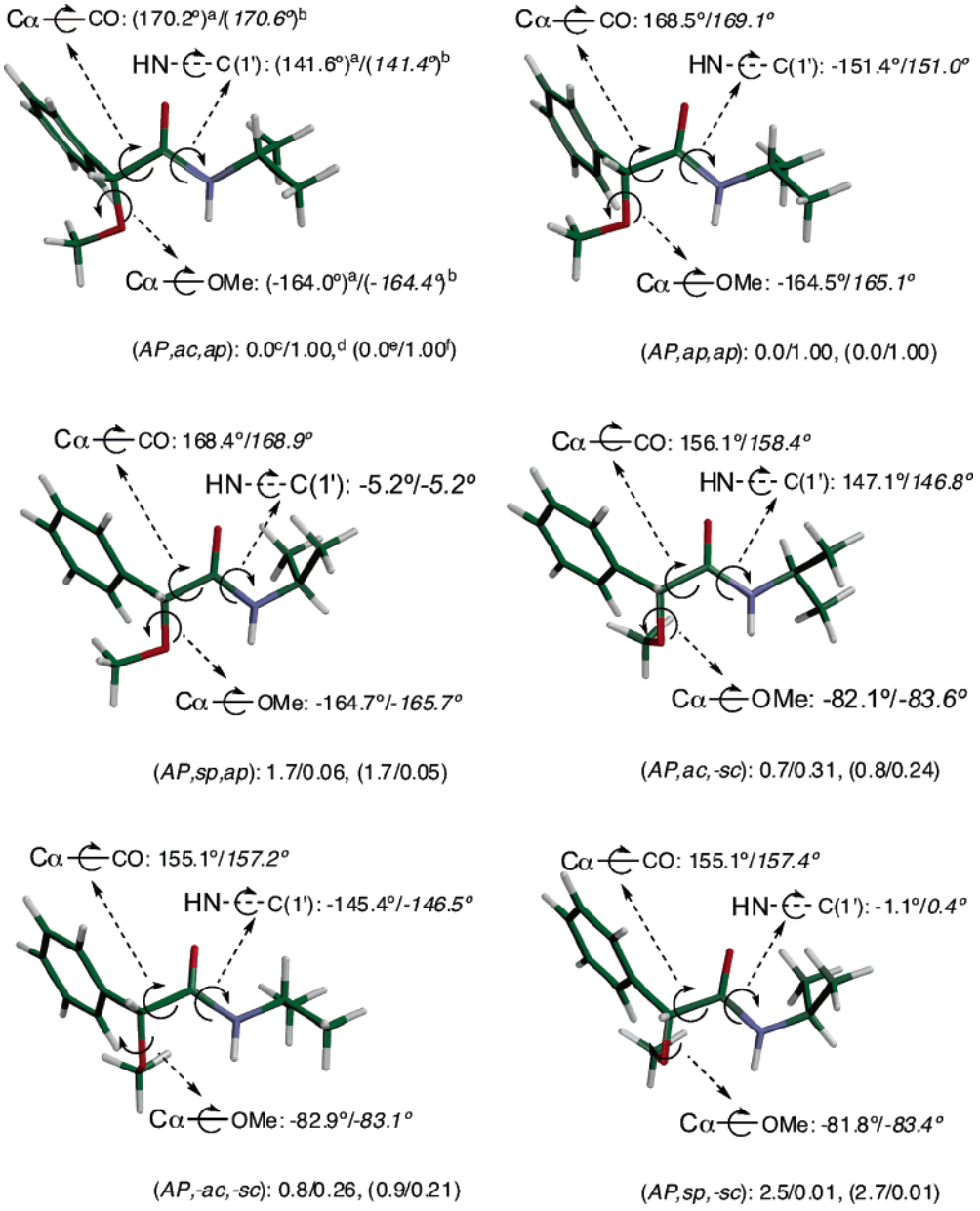


FIGURE 11. Geometries, relative energies, relative populations, and relevant torsional angles for the antiperiplanar conformations of the (*R*)-MPA amide of propan-2-amine (**10**). Torsion angles (in degrees) in the (a) gas phase and (b) Onsager model; relative energies in kcal/mol (B3LYP/landL2DZ); and relative polpulations (Boltzmann, 298.15 K) in the (c,d) gas phase and (e,f) Onsager model, respectively.

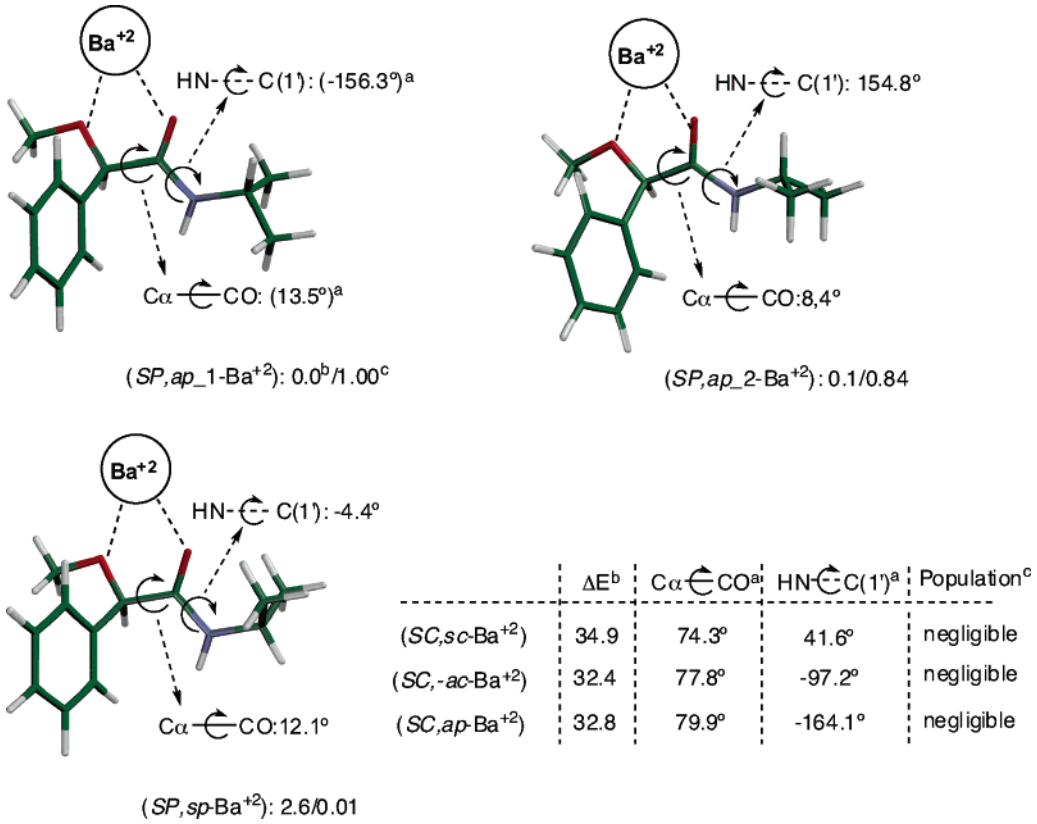
about 5.4 D) than for AP conformations ($\mu \approx 4.2$ D). The stabilization of the SP conformations by the interaction with the solvent is, however, not sufficient for these conformations to contribute substantially to the total population at 298.15 K. As shown in Table 2, the relative energies of the SP conformations are larger than 5.0 kcal/mol, and consequently, the populations at 298.15 K, calculated by the Boltzmann distribution, are negligible. It is worth noticing that the relative energies for the AP conformations do not vary significantly when going from the gas phase to solution. This is because the dipole moment of the molecule has almost the same value in the six AP conformations.

TABLE 2. (a) Relative Energies[a] (in kcal/mol), (b) Relative Populations,[b] and Relevant Torsion Angles (in degrees) for the Conformations of the (*R*)-MPA Amide of Propan-2-amine (10)

		torsion angles (deg)			
conformer	Δ*E*	(Me)O−Cα−C=O	H−N−C(1)−H	Me−O−Cα−**C**(=O)	population
(SP,ac,sc)	5.7	28.3	149.5	61.3	negligible
(SC,−ac,sc)	5.8	32.1	−144.1	−60.9	negligible
(SC,sp,sc)	7.7	30.5	2.6	61.6	negligible
(SC,ac,ap)	6.2	63.1	143.9	172.4	negligible
(SP,−ac,ap)	6.1	66.9	−149.6	172	negligible
(SC,sp,ap)	8.1	66.0	−3.0	172.3	negligible

[a] All calculations were performed with the B3LYP/LanL2DZ basis set. [b] Values calculated from the Boltzmann distribution at 298.15 K.

(17) (a) Fielding, L. *Tetrahedron* **2000**, *56*, 6151−6170. (b) Gil, V. M. S.; Oliveira, N. C. *J. Chem. Educ.* **1990**, 473−478.
(18) Hanna, M. W.; Ashbaugh, A. L. *J. Phys. Chem.* **1964**, *68*, 811−816.
(19) Klyne, W.; Relog, V. P. *Experientia* **1960**, *16*, 521−523.



	ΔE[b]	Cα-CO[a]	HN-C(1')[a]	Population[c]
(*SC,sc*-Ba^{+2})	34.9	74.3°	41.6°	negligible
(*SC,-ac*-Ba^{+2})	32.4	77.8°	-97.2°	negligible
(*SC,ap*-Ba^{+2})	32.8	79.9°	-164.1°	negligible

FIGURE 12. (a) Torsion angles in the gas phase (in degrees), (b) calculated relative energies (B3LYP/landL2DZ) (in kcal/mol), and (c) relative populations (Boltzmann, 298.15 K) in the gas phase for the conformations of the complexes of the (*R*)-MPA amide of propan-2-amine with Ba^{2+}.

The results obtained for the complexes of the (*R*)-MPA amide of propan-2-amine with Ba^{2+} are given in Figure 12. As for the complexes of the MPA ester with Ba^{2+} and Mg^{2+},[20] in general, the calculations including solvent effects showed convergence problems, and so we present only the gas-phase results. In all of these optimized structures, the MeO—CC(=O) fragment presents only one orientation. Therefore, only the OC—CO and the HN—CH torsion angles were taken into account to name the conformers. As for the complexes of the MPA ester with Ba^{2+} and Mg^{2+},[3c] two different conformations were found for the OC—CO arrangement (SP and SC). The energy difference between these two conformations is very large (~30 kcal/mol), almost 3 times larger than that predicted for the complexes of the MPA ester with Ba^{2+}.[3c] This is an expected result that can be rationalized from basic concepts of valence bond theory. The hybridization of both the amidic N atom and the O(—C=O) atom in the SC Ba^{2+} complex of the MPA amide and in the AC Ba^{2+} (ap Ba^{2+} in ref 3c) complex of the MPA ester, respectively, have a significant sp^2 character. For the latter, the interaction of the O(—C=O) atom with the cation takes place via the sp^2 lone pair, whereas for the former, the interaction occurs basically through the electron pair conjugated with the carbonyl group (weaker interaction). The present results, therefore, point out that, in effect, at 298.15 K, all of the calculated complexes of the MPA amide with Ba^{2+} present an SP conformation. Concerning the HN—CH arrangement in the SP conformations, the calculations predict the ap orientation to be more stable than the sp by about 2.5 kcal/mol.

(20) Onsager, L. *J. Am. Chem. Soc*. **1936**, *58*, 1486−1493.

To summarize, the calculations suggest that the conformational equilibrium for the (*R*)-MPA amide of propan-2-amine favors the AP (OCCO) conformations, but in the presence of Ba^{2+}, the formation of complexes with SP conformations is strongly preferred. At 298.15 K, virtually all of the complexes with Ba^{2+} exhibit an SP (OCCO) conformation.

6. Application to the Assignment of Absolute Configurations of Chiral Primary Amines. To check the general applicability of this chelation process for the assignment of the absolute configurations of amines, its scope, and its limitations, the NMR spectra of a series of (*R*)- and (*S*)-MPA amides derived from primary amines of known absolute configuration, including all kind of structures (acyclic, cyclic, bicyclic, with aliphatic and aromatic substituents, with the presence of other functional groups, etc.), were studied in the absence and in the presence of Ba^{2+}.[21]

Figures 13 and 14[22] show the structures of the amides along with the displacement of the signals produced by the addition of the barium salt, measured as $\Delta\delta^{Ba}$.[11] The signs of these shifts are fully consistent with the selective formation of the Ba^{2+} chelate with the SP conformer and the corresponding increase in its population. In all cases, substituents at one side of the chiral center move to higher field upon addition of Ba^{2+}, whereas those on the other side shift to lower field, as shown in Figures 2 and 3. Thus, a regular distribution of the signs of

(21) The spectra were recorded in MeCN-d_3, and the Ba^{2+} was added to the NMR tube in the form of dry, finely powdered $Ba(ClO_4)_2$.

(22) A 2:1 molar ratio of $Ba(ClO_4)_2$ to amide is enough to obtain satisfactory $\Delta\delta^{Ba}$ values, as shown in Figure 13. Nevertheless, larger $\Delta\delta^{Ba}$ values can be obtained if the salt is added until saturation (see Figure 14 and Figure 2-SI in the Supporting Information).

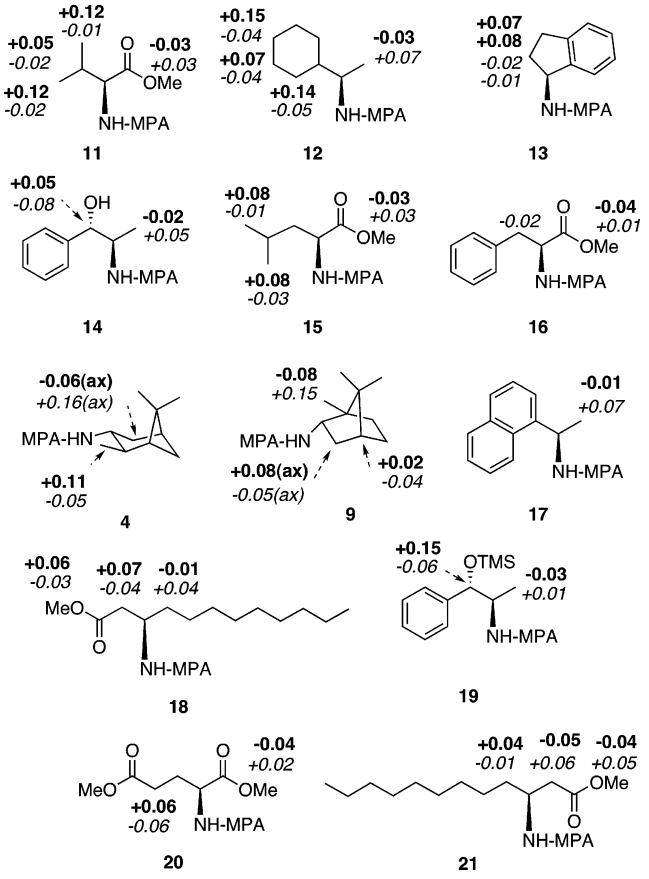


FIGURE 13. Selected $\Delta\delta^{Ba}$ values (ppm) obtained from the ^{1}H NMR spectra (MeCN-d_3) of the (*R*)- (in bold) and (*S*)- (in italics) MPA amides of structurally representative chiral amines upon the addition of 2 equiv of $Ba(ClO_4)_2$ into the NMR tube.

$\Delta\delta^{Ba}$, which are positive for one side of the chiral center and negative for the other, is obtained.

These results demonstrate that the signs of $\Delta\delta^{Ba}$, obtained with either (*R*)-MPA or (*S*)-MPA, can be used to correlate the position of the phenyl group of the auxiliary agent (MPA of known configuration) with the spatial position of the L_1 and L_2 substituents of the amine chiral center and therefore of its absolute configuration. This is so because the amine substituent that faces the phenyl group (the one under its shielding cone) in the AP conformer (i.e., L_2 in Figure 3a or L_1 in Figure 3b) undergoes a downfield shift (negative $\Delta\delta^{Ba}$ value) upon the addition of the barium salt because of the increase of the population of the SP conformer. The other substituent (i.e., L_1 in Figure 3a or L_2 in Figure 3b) undergoes the opposite phenomenon, experiencing an upfield shift (positive $\Delta\delta^{Ba}$ value). It is important to point out that this correlation operates with the (*R*)- and (*S*)-MPA derivatives, and therefore, the assignment can be carried out using only one of those derivatives, either the (*R*)- or the (*S*)-MPA amide, which constitutes a clear advantage when compared to the usual procedures that require the preparation of both MPA derivatives.

As a guide to researchers interested in the use of Ba^{2+} chelation shifts for the assignment of the absolute configuration of α-chiral primary amines, we present a stepwise summary of the procedure in Figure 15: The amine (unknown configuration) is derivatized either with (*R*)- or with (*S*)-MPA. The ^{1}H NMR spectrum of the resulting MPA amide is recorded in MeCN-d_3, and the signals of L_1 and L_2 are unambiguously assigned. A

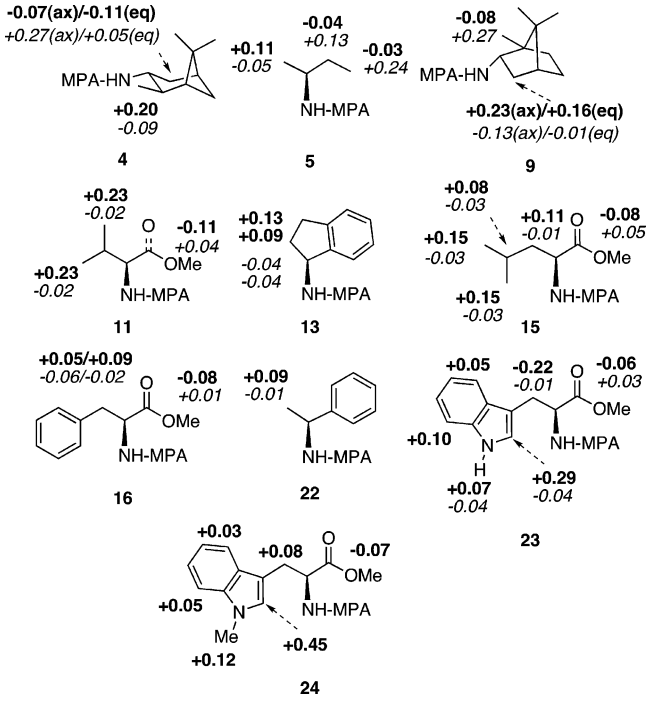


FIGURE 14. Selected $\Delta\delta^{Ba}$ values (ppm) obtained from the ^{1}H NMR spectra (MeCN-d_3) of the (*R*)- (in bold) and (*S*)- (in italics) MPA amides of structurally representative chiral amines upon the addition of $Ba(ClO_4)_2$ into the NMR tube until saturation.

second spectrum is recorded after solid anhydrous $Ba(ClO_4)_2$ is added to the NMR tube until saturation,[21] and the signals of L_1 and L_2 are assigned once more. Then, the $\Delta\delta^{Ba}$ values and signs are calculated, and the graphical models shown in Figure 15 are used to place L_1 and L_2 in space in accordance with the signs (positive or negative) of $\Delta\delta^{Ba}$.

7. Scope and Limitations. As the shifts employed for the assignments are based on the selective formation of the barium-(II) complex, the presence in the substrate of functional groups (i.e., carbonyl and NH groups)[23] that could compete in the formation of the required complex might pose a limitation on the application of the method. In this sense, it is important to realize that Figures 13 and 14 show a number of amines with additional carbonyl (**11**, **15**, **16**, **18**, **21**) and NH (**23**, **24**) groups and that, upon addition of Ba^{2+}, they behave according to the model of Figure 3. However, caution should be taken in the case of amines bearing a 1,4-ketoester moiety. Inadequate shifts have been reported in those cases,[24] most likely because of the competing complexation brought about by the extra carbonyls.

8. Conclusion. We have shown that the absolute configuration of an α-primary amine can be assigned by NMR monitoring of the changes produced upon addition of $Ba(ClO_4)_2$ to either its (*R*)- or (*S*)-MPA amide in MeCN-d_3. A representative number of amines of known configuration and diverse structural features have been used to demonstrate the general applicability of this method and to assess its scope and limitations.

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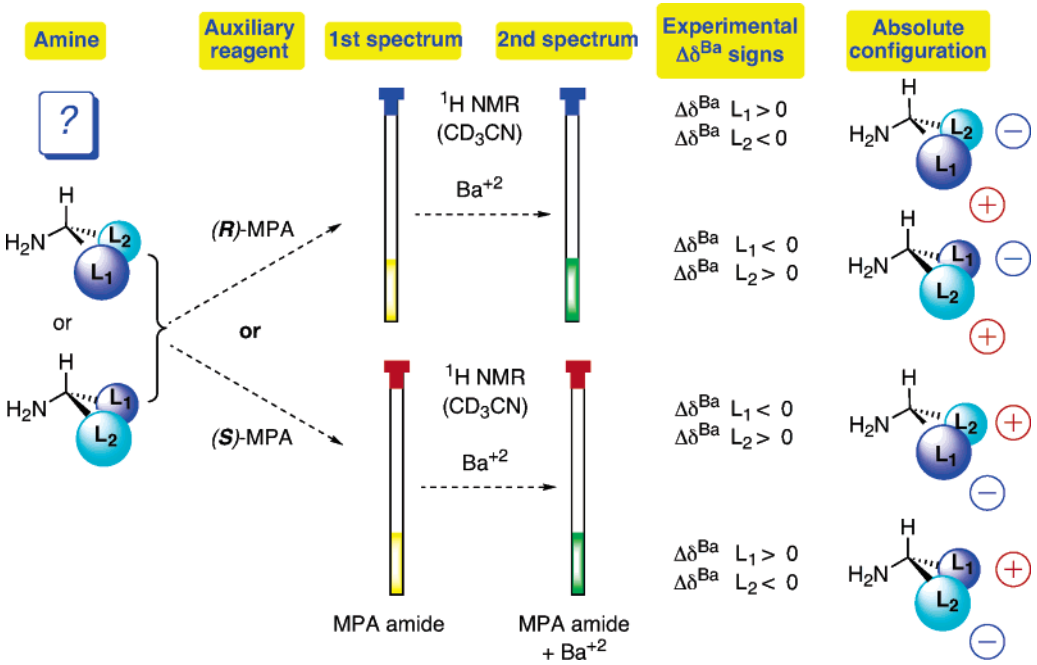

FIGURE 15. Diagram to deduce the absolute configuration of an α-chiral primary amine from the $\Delta\delta^{Ba}$ experimental signs of either the (*R*)- or the (*S*)-MPA amide.

High-level theoretical calculations and experimental data (CD, NMR) support the preferential chelation of one of the conformers (SP) of the MPA amides with the Ba^{2+} cation. This change is transmitted via an aromatic shielding effect to the NMR spectra, where the modifications in the chemical shifts of the L_1/L_2 substituents of the amine are measured as $\Delta\delta^{Ba}$ values.

This procedure is fast, reliable, and inexpensive. It requires a very small amount of sample, only one derivatization with one enantiomer of the auxiliary agent, and the recording of just two ^{1}H NMR spectra at room temperature. It represents a great advantage in relation to the previous procedures available to date that require two derivatizations, twice the amount of sample, and the use of two enantiomers of the auxiliary agent. Unpublished results indicate that the "mix-and-shake" method[25] can also be adapted to the Ba^{2+} complexation procedure.

A graphical model is presented to facilitate the assignment of the absolute configurations of amines from the NMR spectra.

Experimental Section

Computational Methods. Density functional theory (DFT) calculations were performed to study the conformational preferences of the (*R*)-MPA amide of propan-2-amine (used as a model compound) as well as its complexes with Ba^{2+}. In particular, we employed the B3LYP method, which combines Becke's three-parameter nonlocal hybrid exchange potential[26] with the nonlocal correlation functional of Lee, Yang, and Parr.[27] This formalism has been found to be very reliable in the description of ion−molecule complexes.[28] The basis set employed in the calculations was the standard LanL2DZ basis set, which consists of the Dunning/Huzinaga full double-ζ (D95)[29] functions for first row and the Los Alamos effective core potentials plus double-ζ functions on Na−Bi.[30−32]

For the conformers of the (*R*)-MPA amide of propan-2-amine, solvent effects were considered using the Onsager model,[20,33] which considers a polarizable reference molecule as being in vacuum in a spherical cavity. The surroundings of the molecule are treated as a continuum with the macroscopic dielectric constant of the solvent (ϵ = 36.64 for acetonitrile at room temperature). The reference molecule is treated as a point dipole placed in the center of the cavity. A dipole in the molecule will induce a dipole in the medium, and the electric field applied by the solvent dipole will, in turn, interact with the molecular dipole, leading to net stabilization. With this model, full geometry optimizations were performed by using the self-consistent reaction field method.[33] Attempts were made to calculate the conformational energies for the complexes of Ba^{2+} using the Onsager solvation model, but in general, success was not achieved. All calculations were performed with the Gaussian 98 series of programs.[34]

General Procedures. The MPA amides were prepared by treatment of the amine (1.0 equiv) with the corresponding (*R*)- and (*S*)-MPA (1.0 equiv) in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 1.2 equiv) and DMAP (1.0 equiv) in dry CH_2Cl_2 and under a nitrogen atmosphere. The reaction was stirred at room temperature for 2 h. The organic layer was then washed sequentially with water, HCl (1 M), water,

(25) These results will be published elsewhere. The mix-and-shake method is described in ref 4.

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$NaHCO_3$ (saturated), and water. Next, it was dried with Na_2SO_4 (anhydrous) and concentrated under reduced pressure to yield the MPA amide. Final purification was achieved by HPLC (μ-Porasil, 3 mm × 250 mm or Spherisorb S5W 5 μm, hexanes/ethyl acetate). All compounds were characterized by optical rotation, NMR spectroscopy (1D, 2D), and MS (EI).

For experimental details on compounds **9**, **11**, **15**, and **17**, see ref 5a.

General Procedure for Configuration Assignment. The amine is reacted with either the (*R*)- or the (*S*)-MPA reagent, the spectrum of the resulting MPA amide is recorded in MeCN-d_3 (i.e., 5 mg of amide in 0.5 mL of MeCN-d_3), and the signals of L_1 and L_2 are assigned. Solid anhydrous $Ba(ClO_4)_2$ is added to the NMR tube until saturation is attained (about 200 mg per tube), and a new spectrum is recorded. The signals are assigned, and the $\Delta\delta^{Ba}$ values and signs are calculated. The models shown in Figure 15 are used to place L_1 and L_2 in space in accordance with the signs of $\Delta\delta^{Ba}$.

NMR Spectroscopy. ^{1}H and ^{13}C NMR spectra of samples in $CDCl_3$ were recorded at 500 and 250 MHz. Chemical shifts (ppm) are internally referenced to the TMS signal (0 ppm) in all cases. *J* values are recorded in hertz.

1D ^{1}H NMR Spectra. Size, 32 K; pulse length, 2.8 μs (30°); 16 acquisitions.

1D ^{13}C NMR Spectra. Size, 64 K; pulse length, 3.5 μs (30°); 1024 acquisitions.

2D COSY Spectra. Sequence: D1−90−t1−90−t2; relaxation delay D1 = 0.5 s; 90° pulse, 8.5 μs.

2D NOESY Spectra. Sequence: D1−90−t1−90−τ_{mix}−90−t2; relaxation delay D1 = 0.5 s; mixing time (τ_{mix}) = 0.5s, 90° pulse, 8.5 μs; TPPI mode, NS = 64.

(−)-Isopinocampheyl-(*R*)-2-methoxy-2-phenylacetamide [(*R*)-4]. $[\alpha]_D$= −96.20 (*c* = 0.005, $CHCl_3$); ^{1}H NMR (250.13 MHz, $CDCl_3$) δ (ppm) 0.91 (d, *J* = 9.74 Hz, 1H), 1.02 (s, 3H), 1.15 (d, *J* = 7.22 Hz, 3H), 1.48 (ddd, *J* = 2.19, 6.28, 13.97 Hz, 1H), 1.78−1.90 (m, 2H), 1.93 (m, 1H), 2.41 (m, 1H), 3.37 (s, 3H), 4.26 (m, 1H), 4.61 (s, 1H), 6.62 (br, *J* = 9.11 Hz, 1H), 7.27−7.42 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) 21.7, 23.7, 28.4, 37.4, 35.6, 38.8, 41.4, 46.6, 47.6, 48.1, 57.6, 84.1, 127.3, 128.7, 128.9, 137.7, 170.0; MS (EI) *m*/*z* % 301 (M^+).

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Supporting Information Available: Experimental section [computational methods (level of theory, specific program, basis set, Cartesian coordinates, and computed total energies of optimized structures), general procedures, general procedure for configuration assignment, NMR spectroscopy, spectroscopic data for compounds (*S*)-**4**, (*R*) and (*S*)-**5**, (*R*)- and (*S*)-**12**, (*R*)- and (*S*)-**13**, (*R*)- and (*S*)-**14**, (*R*)- and (*S*)-**18**, (*R*)- and (*S*)-**19**, (*R*)- and (*S*)-**20**, (*R*)- and (*S*)-**21**, (*R*)- and (*S*)-**22**, (*R*)- and (*S*)-**24**)]. Figures 1-SI and 2-SI. This material is available free of charge via the Internet at http://pubs.acs.org.

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